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REVIEW ARTICLE

Vitamin D hormone: A multitude of actions potentially influencing the physical function decline in older persons

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Vitamin D, a secosteroid (pro)-hormone, has been traditionally considered as a key regulator of bone metabolism, and calcium and phosphorous homeostasis through a negative feedback with the parathyroid hormone. However, during the last 20 years, the role played by vitamin D has been largely revised by recognizing its pleiotropic action on a wide spectrum of systems, apparatuses and tissues. Thus, vitamin D has growingly been involved as a primary determinant of biological modifications and specific clinical conditions. The effect of vitamin D on skeletal muscle and related outcomes (including physical function decline and disability) is surely one of the most relevant to study in the context of global aging. In the present review, the subclinical and clinical consequences of vitamin D deficiency/insufficiency, extremely frequent conditions in older age, are described. Special focus is given to skeletal muscle and physical function. Limitations of available scientific evidence on the topic are also discussed. **Geriatr Gerontol Int 2010; 10: ••–••.**

Keywords: aging, physical function, sarcopenia, skeletal muscle, vitamin D.

Introduction

Vitamin D has been traditionally considered as a key regulator of bone metabolism, and calcium and phosphorous homeostasis through a negative feedback with the parathyroid hormone.[1,2] It is also well-established that vitamin D deficiency causes rickets in children and osteomalacia and osteoporosis in adults.

The history of vitamin D began in ancient times. Bone deformities among infants due to malnourishment were first described by Soranus of Ephesus and Galen of Pergamum, two physicians practicing medicine in Ancient Rome in the 2nd century. However, the first clear descriptions of rickets were provided by Daniel Whistler in 1645, and by Francis Glisson in 1650 in England, where this condition was endemic at the time; it was even called *morbus anglicus*, or "the English disease". At the beginning of the 20th century, with the development of experimental research and the discovery of vitamins by Sir Patrick Gowland Hopkins and Christiaan Eijkman (who shared the 1929 Nobel prize in Physiology for this), the study of rickets and vitamin D received a considerable boost, till the introduction in 1924 of irradiated milk and bread in the USA which nearly eradicated rickets.[3,4]

Today, approximately 1 billion persons, mostly elders, worldwide present vitamin D deficiency.[1] The prevalence of low vitamin D concentrations in subjects older than 65 years of age has been estimated at approximately 50%,[5–8] but this figure is highly variable because it is influenced by sociodemographic, clinical, therapeutic and environmental factors.

A large and growing body of evidence suggests that vitamin D is not only critical for bone tissue and calcium

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metabolism, but may also represent a crucial determinant for the development of major (sub)clinical conditions and health-related events.[1,9,10] In particular, the hypothesis that vitamin D may represent a relevant factor influencing the disabling process has been proposed by several studies.[11,12] In this review, we discuss current knowledge about the multidimensional actions of vitamin D and its supplementation in the organism, having a special focus on its effects on skeletal muscle and physical function.

Physiology and metabolism

The primary source of vitamin D (up to 95%) is constituted by ultraviolet B radiation, those with a wavelength ranging between 290 and 315 nm, from sunlight. In fact, it has been estimated that the exposure of arms and legs to sunlight for 5–10 min at midday during the first summer months may provide approximately 3000 IU of vitamin D_2 to a subject with light pigmentation of the skin.[1] Sunlight radiations penetrate into the skin and convert the precursor 7-dehydrocholesterol into cholecalciferol or vitamin D_3. There is also another common form of vitamin D that is vitamin D_2 or ergocalciferol, which has the same metabolic meaning of the former, but it has vegetal origins. Vitamin D is then first metabolized in the liver into 25-hydroxy-vitamin D or calcidiol, then in the kidneys by the 25-hydroxy-vitamin D-1α-hydroxylase, a mitochondrial enzyme closely regulated by the parathyroid hormone.[13] The result of this metabolic pathway is the production of the active form 1,25-dihydroxy-vitamin D or calcitriol (Fig. 1). Calcitriol is approximately 500–1000-fold more active than its precursor 25-hydroxy-vitamin D, but the latter is usually measured to estimate the systemic vitamin D status for several reasons. First of all, circulating concentrations of calcitriol are extremely low, approximately 1000-fold less than calcidiol. Moreover, 25-hydroxy-vitamin D is more stable and characterized by a longer half-life (~2–3 weeks) compared to the 1,25-dihydroxy-vitamin D metabolite (~4–6 h). When circulating vitamin D concentrations are low, intestinal calcium and phosphorus absorption decreases and parathyroid hormone levels increase. This latter, besides promoting calcium resorption in the kidneys, also stimulates the immediate production of 1,25-dihydroxy-vitamin D. Thus, with the onset of vitamin D insufficiency, the consequent increase of the parathyroid hormone artificially inflates 1,25-dihydroxy-vitamin D concentrations, potentially providing misleading results on the real vitamin D status.[14]

As mentioned above, the amount of vitamin D mainly derives from sunlight exposure. In fact, the vitamin D dietary intake is usually inadequate and well below the daily requirements of the organism (Table 1). Among foods, only some types of fish are able to provide a reasonable amount of vitamin D_3 (~100–1000 IU for 100 g).[1,15–17] If not artificially fortified, other foods/beverages (including milk, cheeses and fruit juices) provide very low, if any, amounts of vitamin D.[1,15–17] Consequently, the recommended daily dietary intake of vitamin D_3 (i.e. a minimum of 800 IU),[1] it is very rarely

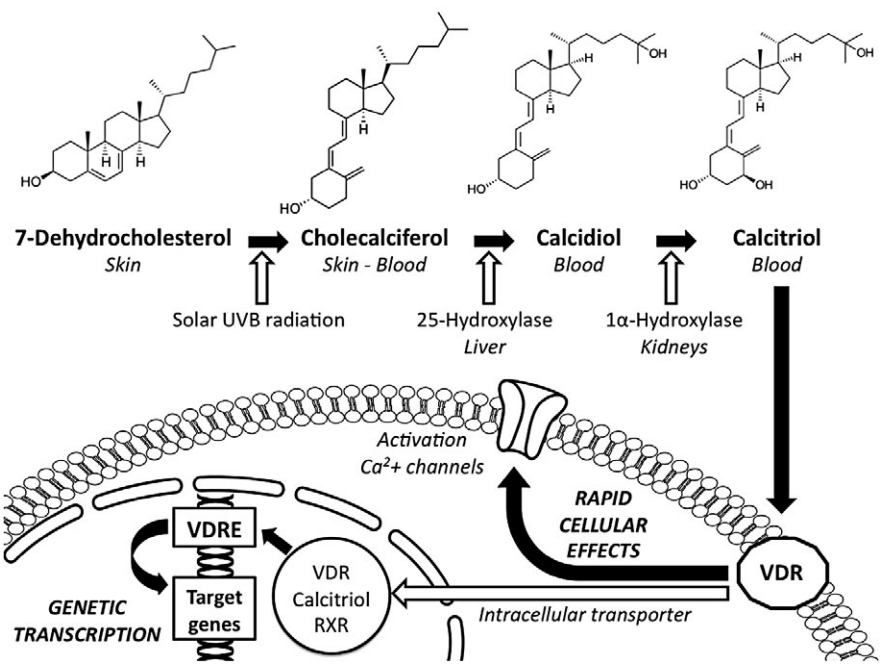

Figure 1 Vitamin D hormone modifications and its cellular effects. RXR, retinoic receptor; UVB, ultraviolet B; VDR, vitamin D receptor; VDRE, vitamin D receptor elements.

Table 1 Examples of food sources of vitamin D[15]

	Amount of vitamin D (IU)
Sunlight exposure of arms and legs for 5–10 min at midday during the first summer months	3000
Cod liver oil (1 tablespoon, 13.6 g)	1360
Wild salmon, cooked dry heat (100 g)	451
Mackerel, canned (100 g)	292
Tuna, light, canned in oil (100 g)	269
Sardines, canned in oil (100 g)	193
Whole milk with added vitamin D (1 cup, 244 g)	124
Cod, cooked, dry heat (100 g)	46
Cereals, corn flakes, low sodium (1 cup, 25 g)	36
Egg (medium size, whole, raw, 44 g)	22
Mozzarella cheese, whole milk (100 g)	16
Chicken tenders, cooked in conventional oven (100 g)	10
Beef steak, top sirloin, cooked, broiled (100 g)	7
Whole milk without added vitamin D (1 cup, 244 g)	5
Cabbage, boiled (100 g)	0
Italian bread (100 g)	0
Lettuce, green leaf (100 g)	0
Orange (1 medium fruit, 131 g)	0
Olive oil (1 tablespoon, 13.5 g)	0
Potato, boiled without skin (medium size, 167 g)	0
White rice, long-grain, parboiled, (un)enriched, cooked (100 g)	0

One microgram of dietary vitamin D is equivalent to 40 IU.

reached by common diets. Cholecalciferol is not stored in the muscle and fat tissues until its serum concentrations are above 20–50 ng/mL, and only above this threshold is the organism able to use its vitamin D reserves to work independently of dietary intakes or sunlight exposure. Therefore, because these 25-hydroxy-vitamin D concentrations are difficult to reach, especially in older persons, the organism usually works in a reserve status.[18,19] From all this, it becomes clear why the maintenance of adequate vitamin D concentrations necessarily goes through a reasonable exposure to sunlight and vitamin D supplementation.[1,10,20]

During the last 20 years, the role played by vitamin D has been largely revised by recognizing its pleiotropic action on a wide spectrum of systems, apparatuses and tissues. Moreover, 1,25-dihydroxy-vitamin D is not only produced by kidneys with the endocrine function of regulating calcium and phosphorous homeostasis. It has been demonstrated that the active form of vitamin D is also produced by several other tissues with autocrine pattern and local effects.[21] These findings obviously led to the conjecture that vitamin D is potentially involved in a number of extra-bone subclinical and clinical conditions, and a possible determinant of major clinical outcomes. Thus, it is not surprising that vitamin D is today considered as a hormone rather than as a vitamin in the true meaning of the word.[1,22] Different from most of the other vitamins, the active form of vitamin D (i.e. 1,25-dihydroxy-vitamin D) is not a cofactor of enzymatic reactions or an antioxidant, but a fat-soluble secosteroid hormone. The only "vitamin" property left for this micronutrient is maybe the capacity to determine the onset of clinical conditions for insufficient dietary intake and consequent deficiency.[23]

Vitamin D receptor

The 1,25-dihydroxy-vitamin D exhibits a wide spectrum of actions through the interaction with a specific receptor (i.e. vitamin D receptor, VDR), member of a superfamily of nuclear receptors.[24] Vitamin D easily passes through biological membranes. After being transferred into the nucleus by an intracellular transporter protein, the 1,25-dihydroxy-vitamin D:VDR complex combined with the retinoic receptor constitutes a heterodimer able to bind the vitamin D responsive elements (VDRE) located on specific promoter regions of the target genes, modulating their expressions.[25] Recently, the existence of a second vitamin D mechanism of action has been hypothesized. In fact, the slow genetic transcription pathway, which requires hours to days, cannot explain alone the evidence of rapid onset cellular responses induced by vitamin D. It is likely that an alternative receptor for vitamin D located on the cellular membrane[26,27] is able to promote the activation of second messengers (such as cyclic adenosine monophosphate [AMP] or mitogen-activated protein kinase [MAPK]) influencing calcium channels and determining immediate cellular effects (Fig. 1).[21] This may simply be the VDR itself after migration from the nucleus to the cellular membrane.[28]

The *VDR* gene is located on the chromosome 12 (12q13,11). The existence of several *VDR* gene polymorphisms able to modify its expression and determine different phenotypes and biological responses has been demonstrated. Regarding physical function, two *VDR* polymorphisms are of special interest because they are not only able to affect bone mineral density, but also body composition, muscle strength and the response to physical exercise:[29–31] *FokI* involving a T/C substitution on exon 2 of the *VDR* gene, and *BsmI* due to the

modification of the final part 3′ of the *VDR* gene. The identification of these polymorphisms and the demonstration of their effects on muscle and function supports the hypothesis of a direct role played by vitamin D in determining sarcopenia, age-related physical decline and disabling process.

Risk factors for vitamin D deficiency

Numerous endogenous and exogenous risk factors have shown to affect the serum concentrations of vitamin D. The most relevant are:

- Sex. It has been reported that women are more likely to develop hypovitaminosis D than men.[32]
- Sunlight exposure, latitude, and seasonal variations. Vitamin D concentrations are directly associated with the exposure to solar ultraviolet B photons. Therefore, vitamin D concentrations tend to be lower during the winter season[7,33,34] and at higher degrees of latitude (e.g. above 35°N, little or no vitamin D can be produced from November to February).[1,9,35]
- Dark skin pigmentation. African-Americans present an increased risk of low vitamin D concentrations compared to Caucasians, independent of age.[36]
- Diet.[1]
- Obesity. The sequestration of vitamin D in body fat reduces its availability.[1] Moreover, the existence of a relationship between vitamin D, inflammation and adipose tissue has been hypothesized.[37]
- Impaired renal function.[38]

Interestingly, all these risk factors tend to become more and more frequent with increasing age, easily explaining why hypovitaminosis D is a typical condition in the elderly. Moreover, the aging process itself predisposes to vitamin D deficiency, especially because of the age-related skin structure modifications. In fact, a progressive decline in the cutaneous capacity to synthesize vitamin D from ultraviolet B radiations[35,39] (at least partly due to the reduction of 7-dehydro-cholesterol in the skin) and an increased resistance of target organs to the vitamin D action (probably due to the reduction of VDR[40] or post-receptorial modifications[41])[42] have been described.

Pleiotropic action of vitamin D

Approximately 50 years ago, Elkeles[43] hypothesized a shift of the calcium from bones, representing the primary deposit of this element in the organism, to soft tissues occurring with aging. This hypothesis, also called the "theory of calcium mobilization", was proposed to explain some calcium-related conditions typical of older age, such as osteoporosis, atherosclerosis and hypertension. Although this theory may seem today too simplistic, it still has some value if the multitude of actions played by calcium and, in parallel, by vitamin D in the organism are taken into account. The systemic hormonal role of vitamin D is today largely supported by the evidence of VDR and 25-hydroxy-vitamin D-1α-hydroxylase enzyme in numerous tissues and cells (e.g. bone, brain, prostatic, intestinal, muscular tissues and immune cells).[1,44] Moreover, it has recently been estimated that the 1,25-dihydroxy-vitamin D is able to modulate the expression of more than 200 genes involved in a wide spectrum of mechanisms, from cell proliferation to cellular differentiation, from apoptosis to angiogenesis.[1,45]

Because vitamin D is characterized by such a multidirectional action in the organism, its effects need to be systemic rather than local or tissue-specific. This obvious conclusion is supported by reports showing that vitamin D is predictive of a wide spectrum of major clinical outcomes. For example, Autier and Gandini[46] recently reported a 7% decreased risk of mortality from vitamin D supplementation in a meta-analysis of 18 randomized clinical trials. Vitamin D has also been indicated as a critical determinant of cardiovascular health status.[47] This statement finds support by evidence from studies on knockout animals without VDR, which are consequently not influenced by vitamin D, showing development of hypertension and cardiac hypertrophy.[48] Moreover, heart failure is a well-recognized consequence of rickets,[49] and several studies have shown that low serum concentrations of 25-hydroxy-vitamin D are associated with increased risk of cardiovascular death.[50–52] Vitamin D has also been involved in the development and function of the central nervous system. Studies in animal models have demonstrated that vitamin D treatment in rats is able to increase neuron density in the hippocampus.[53] Consistently, a low expression of VDR has been reported in hippocampal cells of Alzheimer's disease patients.[54] Recently, Wilkins *et al*.[55,56] have shown reduced cognitive function in older persons with low vitamin D concentrations. Moreover, a large (and growing) body of evidence on vitamin D is currently devoted to demonstrate a strong link with multiple sclerosis.[57–59] Interestingly, the reduction of nervous conduction velocity due to low vitamin D concentrations and the restoration of the former by vitamin D supplementation have been reported.[60,61] The 1,25-dihydroxy-vitamin D is also a potent immunomodulator,[62,63] as demonstrated by its capacity to stimulate the production of cathelicidin, a peptide able to destroy several infective agents including *Mycobacterium tuberculosis*.[64] A recent study demonstrating vestibular dysfunction in mice without VDR is interesting, especially because of the potential future implications on humans.[65] Finally, vitamin D has been associated with psychiatric conditions,[66,67] metabolic syndrome[68] and cancer (although, in this latter case, with some uncertainties).[69] If considered as a whole with the geriatrician's eyes, all this evidence proposes an exceptional

number of possible explanations in the link between vitamin D and physical function. In fact, the pleiotropic action of vitamin D in our organism may critically determine the proper physical function which, ultimately, is the result of a multidimensional interaction among systems, apparatuses and organs.

Skeletal muscle and physical function

The hypothesis that vitamin D is involved in the prevention of sarcopenia, physical decline and disability is extremely interesting. The idea that vitamin D might be linked to muscular function was initially proposed several decades ago, in particular during the years between the two World Wars. Several clinical studies, especially conducted in Germany and the Soviet Union, were aimed at demonstrating the effects of ultraviolet radiation on physical performance.[70,71] In 1927, a controversy arose in the sports world when the German Swimmers' Association decided to use sunlamps to boost its athletes' performances because it was considered a sort of doping.[71] Gorkin *et al*.[70] demonstrated relevant improvements (~6%) in the 100-m dash speed in four students after ultraviolet radiation compared with matched controls. In 1940, Parade and Otto[71] discussed a series of previous experiments demonstrating that sunlamp irradiation was beneficial on muscle strength, and suggested a systemic effect of ultraviolet irradiation. During the following years, the relationship between muscle and vitamin D was more directly substantiated by case reports describing myopathies in patients with osteomalacia.[72,73] If the myopathy was initially thought to be due to the osteomalacia condition and poor health status, subsequent reports describing relevant beneficial effects (up to the complete regression of myopathy) after vitamin D supplementation reversed the scenario.[74–76] Therefore, muscular symptoms were started to be considered not as an epiphenomenon of hypovitaminosis, but as a direct consequence of it. The identification of VDR in muscular tissue from biopsies performed in animal models,[77] and, more recently, in humans[78,79] has definitively confirmed the presence of a direct interaction between vitamin D and skeletal muscle.

It is likely that proper muscular functioning is determined by an adequate amount of available vitamin D, as suggested by evidence from animal and human models. An altered muscular development has been described in knockout mice without VDR.[80] Consistently, the histological examination of muscle tissue from subjects with osteomalacia is characterized by increased interfibrillar spaces, intramuscular adipose tissue infiltrates and fibrosis.[81] Interestingly, muscle biopsies performed before and after vitamin D supplementation have documented an increased number and section area of type II (or fast) muscle fibers.[82,83] It is noteworthy that this type of fiber is the one more involved in fall prevention, thus providing a possible explanation for data showing a higher tendency to fall in subjects with low vitamin D concentrations. In this context, it is useful to remember some clinical features of subjects with hypovitaminosis D: weakness and/or (especially proximal) muscle pain, unstable gait, difficulties in climbing up stairs or raising from a sitting position on a chair, and generalized loss of muscular mass without relevant sensorial or osteotendineal abnormalities.[84,85] A large body of evidence currently demonstrates that low vitamin D concentrations represent an independent risk factor for falls in older persons.[86–89] However, when studies have tested the effect of vitamin D supplementation on the fall event outcome, results became more contradictory. In fact, together with studies presenting positive findings,[90–92] negative results were reported,[93,94] too. This discrepancy of data can also be confirmed by several recent meta-analyses on the topic.[95–97]

Available evidence about the efficacy of vitamin D supplementation is also controversial when, looking at a different outcome, we consider physical function. In fact, although most of the epidemiological studies support such association[8,55,98–104] with only a few and sometimes partial[105] exceptions,[106] intervention studies are currently far from being definitive.

Current clinical and research issues

It is certain that there are several methodological issues at the basis of available evidence that are, at least partially, responsible for such inability to draw definitive conclusions.[11] First of all, the selection criteria adopted to recruit the study populations may have significantly affected the available evidence. For example, a recent work by Lips *et al*.[107] described a significant improvement of balance after vitamin D supplementation (8400 IU of vitamin D_3 per week for 16 weeks) only in participants with higher mediolateral postural sway at the baseline. Although these trial results are mainly negative for the vitamin D effects on physical performance, on the other hand they suggest that supplementation may be important in patients with clinical signs/symptoms of hypovitaminosis D. Moreover, it is noteworthy that the "severe vitamin D deficiency" exclusion criterion adopted in this trial may have selected a relatively healthier group of participants, thus eliminating from the study sample those subjects more amenable to benefit from the intervention.

A critical issue to consider when evaluating the findings from clinical trials is represented by the adherence to the intervention. Effectively, some of the reported findings were obtained adopting an "intention-to-treat" approach, but several studies were characterized by low levels of adherence to the intervention.[95,96] Moreover, an inadequate length of the follow up/intervention

(sometimes no longer than 6 months) might have contributed to biasing the available evidence.[108] In the attempt to facilitate adherence to the treatment, some studies have recently tested the effects of annual high-dose (300 000–500 000 IU) vitamin D supplementations on falls[94] and fractures,[94,109] but results were not encouraging and even suggested an increased risk of fractures in the intervention arm of the trials. As discussed by Dawson-Hughes,[110] these results do not cancel the large evidence supporting the beneficial effects from vitamin D supplementation, but underline the need for a more cautious approach, especially when considering high-dose and/or long term interventions. It should always be taken into account that, although vitamin D supplementation is relatively safe, the risk of adverse drug reactions, in particular hypercalcemia and its consequences (e.g. nephrolithiasis, gastrointestinal abnormalities, hypertension, arterial stiffness, cognitive impairment, electrocardiographic modifications)[111] is always present,[112] especially in persons with impaired renal function and/or treated with thiazide diuretics.

Last but not least, the reading and comparison of vitamin D studies is hindered by the extreme heterogeneity of cut-points defining its status of deficiency. Over the years and still today, vitamin D deficiency and insufficiency have been defined in multiple ways. The first definitions of minimum serum 25-hydroxy-vitamin D concentrations were likely too low and underestimated the importance of this vitamin. Therefore, over time, these cut-points have progressively been raised. With the increase of the minimum concentrations defining the low vitamin D status, there has been a parallel increase of recommended dietary intakes and supplementation doses over time. In fact, almost every year, normal ranges of vitamin D concentrations have been raised.[113,114] This has not facilitated the methodological homogeneity and, thus, comparability of available clinical trials testing vitamin D supplementation. While, as discussed above, low vitamin D concentrations are quite frequent, vitamin D toxicity, which is characterized by hypercalcemia and hyperphosphatemia, is a very rare condition, mainly caused by a long-term high-dose supplementation.[115,116] Because any excess of cholecalciferol is destroyed by sunlight, prolonged exposure to sunlight cannot cause vitamin D_3 intoxication. The most commonly and currently adopted cut-points to define vitamin D status (more exactly 25-hydroxy-vitamin D)[10,15] are reported in Table 2. Interestingly, both definitions presented in Table 2 define vitamin D severe deficiency using the same cut-point (i.e. 10 ng/mL or 25 nmol/L). A biological rationale for choosing this cut-point is provided by the identification at this level of an inflection in the negative association existing between vitamin D and parathyroid hormone.[117] In other words, when vitamin D is at this concentration or below, parathyroid hormone is suppressed.[117–120] Some authors have also proposed the 30 ng/mL (or 75 nmol/L) cut-point to determine inadequate vitamin D concentrations.[10,21] Below this threshold, the parallel and inverse association between parathyroid hormone and vitamin D is more evident. Unfortunately, the biological support for the definitions of most cut-point definitions (i.e. insufficiency, normal range, toxicity) is not so strong and/or free of controversies.

Table 2 Serum concentrations of vitamin D (25-hydroxy-vitamin D)

Status	ng/mL	nmol/L
Derived from Lee *et al.*[10]		
Severe deficit	<10	<25
Deficit	10–20	25–50
Insufficiency	21–29	51–74
Normal values	30–150	75–375
Toxicity	>150	>375
From the Dietary Supplement Fact Sheet of the National Institutes of Health (NIH) Office of Dietary Supplements[15]		
Deficiency leading to rickets and osteomalacia	<10	<25
Inadequate for bone and overall health	10–14	25–37.4
Adequate for bone and overall health	15–200	37.5–500
Potentially toxic	>200	>500

Conversion factor between conventional (ng/mL) and SI (nmol/L) units is 2.496. Cut-points are rounded to facilitate their use in clinical practice.

Conclusion

Several uncertainties are still currently present about the role that vitamin D plays on physical function, and whether this possible effect may not merely be the indirect manifestation of a poor health status.[101] Therefore, it is crucial that the design and development of new studies are specifically aimed at: (i) defining clinically relevant vitamin D cut-points distinguishing across the different statuses of this biomarker; (ii) evaluating the effects of interventions aimed at the maintenance/improvement of physical function in the elderly; (iii) verifying the preventive effect of such interventions for the main clinical outcomes of geriatric medicine, especially incident disability and institutionalization; (iv) calculating the cost-effectiveness of treatments for vitamin D deficiency; (v) clarifying pathophysiological mechanisms at the basis of the relationship between hypovitaminosis D and adverse events in older persons; and (vi) determining safety and potential adverse events of vitamin D supplementation in older persons. Although

there is apparently a long way still to go, currently available data are overall encouraging. Hopefully, the improvement of our knowledge on vitamin D-related mechanisms will provide a major preventive instrument for older persons.

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